Chapter 3

Antimalarial drug trials involving the ADF

3.1 This chapter considers the extent to which ADF members can provide informed consent to participate in research, and presents information on ADF antimalarial policy. It summarises the consent process undertaken for the antimalarial drug trials during the late 1990s and early 2000s, as well as outlining perspectives on the screening processes, responses to adverse events and participant follow up.

Consenting to participate in research

3.2 The ethics of human research in military populations is addressed in the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Human Research* (National Statement).[1] This outlines the general requirements for seeking individuals' consent to participate in research:

> …consent should be a voluntary choice, and should be based on sufficient information and adequate understanding of both the proposed research and the implications of participation in it.[2]

3.3 Pre-existing relationships between prospective research participants and those involved in facilitating or implementing the research 'may compromise the voluntary character of participants' decisions, as they typically involve unequal status, where one party has or has had a position of influence or authority over the other'.[3] The relationship between a soldier occupying a subordinate position and their senior officer is an example of an unequal relationship.[4]

3.4 The National Statement suggests that an unequal relationship 'always constitutes a reason to pay particular attention to the process through which consent is negotiated'.[5] However, it is not automatically sufficient to prevent research being undertaken, rather, 'you have to think about extra ethical considerations when approving and conducting that research'.[6]

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1 NHMRC, Australian Research Council (ARC) and Universities Australia, *National Statement*, 2007 (updated 2018), Chapter 4.3: People in dependent or unequal relationships, p. 68.

2 *National Statement*, p. 16.

3 *National Statement*, p. 68.

4 Inspector-General of the ADF (IGADF), *Inquiry report into issues concerning anti-malarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*, 2016, p. 23; Australian Government Therapeutic Goods Administration, *Note for Guidance on Good Clinical Practice*, 2000, p. 13.

5 *National Statement*, p. 68.

6 Ms Jillian Barr, Ethics and Integrity, Research Quality and Priorities Branch, NHMRC, *Committee Hansard*, 11 October 2018, p. 13.

Views on whether the ADF should participate in medical research

3.5 The committee heard different perspectives on whether ADF members can truly consent to participate in research.

Opposition to ADF participation

3.6 The participation of ADF members in research was viewed by some submitters, such as Mr Greg Jose, as 'cruel and unethical'.[7] Some veterans suggested that drug trials on ADF members should be prohibited.[8] This was echoed by others including the Royal Australian Regiment (RAR) Association and the wife of a veteran.[9] Colonel Ray Martin (Rtd) opposed mass drug trials as members cannot:

> …give truly informed and voluntary consent and…drug trials with untested or potentially harmful drugs will likely detract from operational effectiveness of the ADF, and or produce ineffective results.[10]

3.7 Mr Benjamin Fleming proposed 'legislation be put to parliament that prevents the testing of drugs on deployed personnel, who, by the mere fact of the environment they are working in, have enough to deal with'.[11] The submission by Associate Professor Quinn on behalf of the Australian Quinoline Veterans and Families Association (AQVFA) further recommended that 'veterans are precluded by law from being engaged as subjects in clinical trials'.[12]

Support for ADF participation

3.8 Other submitters argued that ADF members should not be prohibited from participating in research, because it is vital for advancing medical science and force protection measures, and because members should have the right to choose and to access higher levels of care through trials. Vice Admiral David Johnston AO, Vice Chief of the Defence Force, explained Defence needs to retain:

> ...the ability to conduct clinical studies for improved and emerging medications to be evaluated to ensure they are effective and safe in military populations. It's an accepted scientific fact that studies of therapeutic agents need to be conducted in the population in which they will be used.[13]

3.9 The committee heard from doctors and scientists who agreed, such as Associate Professor Harin Karunajeewa, who stated that the ADF:

> …has both a duty of care to protect and maintain the health of its personnel, and a strategic imperative to maintain the fitness and battle-readiness of its

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7 Mr Greg Jose, *Committee Hansard*, 31 August 2018, p. 2.

8 See Mr Stuart McCarthy, *Submission 94*, p. 11; Name withheld, *Submission 59*, [p. 5].

9 *Submission 96*, [p. 1]; Mrs Susan Armstrong, *Committee Hansard*, 30 August 2018, p. 15.

10 *Submission 92*, [p. 4].

11 *Committee Hansard*, 30 August 2018, p. 32.

12 *Submission 16*, p. 6.

13 *Committee Hansard*, 11 October 2018, p. 45.

> troops. It is therefore perfectly logical and ethically appropriate that the ADF should endeavour to understand what the most effective and safest ways are to protect its troops from the high risks of a potentially debilitating and lethal disease…the best way to find out what works best is to actually perform a test in the population for which the treatment is intended. Clinical trials in the military have done a great deal to improve the health, safety and effectiveness of soldiers throughout modern history. It is in the best interest of all soldiers that they continue.[14]

3.10 Based on evidence from hospitals in the United Kingdom and his own experience conducting trials, Associate Professor Karunajeewa noted that 'clinical trial participants are likely to receive better medical care and have better outcomes to patients receiving routine care'.[15] Mr Mark Reid, coordinator of one of the trials involving the ADF, reiterated this point and noted this trial involved the:

> …only infantry battalion that has ever deployed into a malarious area with no clinical cases [of malaria] in the field. And it wasn't just the drugs that achieved that; it was the actual awareness of having people there with a specific mandate of force protection under a controlled clinical trial.[16]

3.11 Defence rejected 'claims that informed consent is not possible in military populations and the assertion that clinical studies should not be conducted on these personnel'.[17] It underscored its support for individuals' rights to decide whether to participate or not in research, and cautioned any constraints on research:

> …must be balanced against the considerable direct benefits that have been obtained by participants in clinical studies of novel drugs to treat a variety of medical conditions. While some research may not infer direct benefit to the individual, everyone has the right to choose whether or not to participate for their own future benefit, or the benefit of others.[18]

Considerations for future research involving ADF members

3.12 The National Statement identifies that people in unequal relationships 'are vulnerable to being over-researched because of the relative ease of access to them as research populations'.[19] Therefore, it suggested that researchers 'should take account of this vulnerability in deciding whether to seek out members of these populations as

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14 For other examples see: Professor James McCarthy, Professor of Tropical Medicine and Infectious Diseases, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute, *Submission 15*, [p. 12]; Professor Geoffrey Quail, President of the Australian College of Tropical Medicine; *Committee Hansard*, 30 August 2018, p. 44.

15 *Submission 15*, [pp. 12–13].

16 *Committee Hansard*, 30 August 2018, p. 21. This trial compared tafenoquine and mefloquine use in 1 RAR in Timor-Leste in 2000 to 2001.

17 *Submission 1*, p. 27.

18 *Supplementary submission 1.1*, pp. 15–16.

19 NHMRC, ARC and Universities Australia, *National Statement*, p. 68.

research participants'.[20] Similarly, a report by the Inspector-General of the Australian Defence Force (IGADF) into issues concerning some of the trials recommended:

> The ready acceptance by soldiers of advice or encouragement provided to them by military persons in authority, combined with a potential belief that participation in the trial was expected is an issue worthy of further consideration in the conduct of any future medical trials, particularly in the context of a pre-deployment for an overseas operation.[21]

3.13 Defence noted that each time the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) examines a research proposal it considers the issue of informed consent in military populations.[22] DDVA HREC is 'acutely aware' that military personnel may be vulnerable due to their unequal relationships 'and is very stringent in its review of research proposals to ensure that there is no coercion, real or perceived, in the recruitment of participants from the ADF'.[23] Membership of the current DDVA HREC includes a contemporary veteran, Defence health graduate, a lawyer, lay people, a pastoral care member, a civilian clinical care provider and others with experience in the types of research being considered by the DDVA HREC.[24] The DDVA HREC terms of reference establish that 'at least one third of the members are to be external to Defence and DVA'.[25]

3.14 The National Statement further suggests that researchers should:

> …invite potential participants to discuss their participation with someone who is able to support them in making their decision. Where potential participants are especially vulnerable or powerless, consideration should be given to the appointment of a participant advocate.[26]

3.15 The committee did not hear evidence on examples of where participant advocates have been appointed elsewhere.[27]

3.16 AVM Tracy Smart AM recently wrote to DDVA HREC to request that it 'consider additional measures to ensure participants in clinical studies, and particularly

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20 *National Statement*, p. 68.

21 IGADF, *Inquiry report*, 2016, p. vi.

22 Defence, *Submission 1*, p. 33. When the research is deemed to be of low- or negligible-risk, reviews are undertaken by the Joint Health Command Low Risk Ethics Panel, People Research Low Risk Ethics Panel or Defence Science and Technology Low Risk Ethics Panel. Defence and Department of Veterans' Affairs, *The Departments of Defence and Veterans' Affairs Human Research Ethics Committee Terms of Reference*, p. 2, http://www.defence.gov.au/health/hrec/ (accessed 11 October 2018).

23 Defence, *Supplementary submission 1.1*, p. 15.

24 Defence, *Supplementary submission 1.1*, p. 15.

25 *DDVA HREC Terms of Reference*, pp. 2–4,

26 NHMRC, ARC and Universities Australia, *National Statement*, p. 68.

27 Ms Barr, *Committee Hansard*, 11 October 2018, pp. 13–14.

Phase 3 clinical trials, are fully informed of all aspects of the studies and that there is no belief created that Command is endorsing or actively encouraging the study'.[28] AVM Smart suggested initiatives could include providing a standard script to Command and standard briefing materials to prospective participants, and having an external agency observe, monitor, evaluate and report on the consent process.[29]

ADF antimalarial prescribing policies and practices

3.17 Defence provided a summary of its malaria policies since 1990.[30] The committee heard the claim that some ADF members had been prescribed mefloquine as a first-line antimalarial.[31] However, Defence indicated that doxycycline has been the antimalarial medication of choice for prevention since the early 1990s.[32] During the start of the trials, doxycycline was the first line antimalarial, and mefloquine was the next option if doxycycline was contraindicated.[33] If both doxycycline and mefloquine were contraindicated, Atovaquone/proguanil (Malarone™) was the third option. However, at that time Malarone had not been approved for malarial prophylaxis by the Therapeutic Goods Administration (TGA).[34] Defence stated that its 'health policy regarding malaria has consistently provided guidance regarding potential side effects of each antimalarial medication, based on what was known at the time, and on reporting of adverse events'.[35] Guidance on monitoring and reporting adverse effects has been 'refined and expanded over the years'.[36]

3.18 The committee's inquiry largely focused on mefloquine and tafenoquine. VCDF Johnston emphasised that Defence has been cautious in its use of mefloquine, noting it 'has always acknowledged that this drug has side effects and has never used it as a first-line antimalarial medication'.[37] Tafenoquine was only registered in 2018, and, to date, Defence has only permitted its use during the trials.[38]

Loading doses

3.19 The term 'loading dose' refers to the practice of prescribing a higher dose of a medication for a short period at the beginning of a course, before reducing the dose to maintain the level of protection. Defence noted that:

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28 Defence, *Letter form AVM Tracy Smart AM to Mr Ian Tindall, Chair DDVA HREC,* 4 October 2018, [p. 1] (tabled 11 October 2018).

29 *Letter form AVM Tracy Smart AM to Mr Ian Tindall*, [pp. 1–2].

30 Defence, *Submission 1*, Annex R, [pp. 229–233].

31 For example, see Mr Brian McCarthy, *Submission 73*, pp. 3–5.

32 *Submission 1*, p. 36.

33 *Submission 1*, pp. 10, 36. See Defence, *Submission 1*, Annex S, [pp. 234–249].

34 Defence, *Submission 1*, Annex S, [p. 239].

35 Defence, *Submission 1*, p. 39.

36 Defence, *Submission 1*, p. 39.

37 *Committee Hansard*, 11 October 2018, p. 45.

38 Defence, *Submission 1*, p. 37.

> Taking a three day loading dose at the start of a course of mefloquine when used for prevention is standard Defence practice. A three day loading dose was also used for those taking tafenoquine during the studies.[39]

3.20 The committee heard that a 1985 study sponsored by the World Health Organization found a mefloquine loading dose for the treatment of malaria caused some mild and transient side effects, but concluded the drug was highly effective, well tolerated and safe.[40] It also heard that another study[41] compared 250 milligrams (mg) weekly versus 250 mg daily for three days (loading dose), and found:

> …more sleep disturbances, vivid dreams and depressive feelings in the patients who took the loading dose, which diminished over time. The authors concluded that the loading dose should be considered as an option for short-term travellers or military personnel...[42]

3.21 The committee heard some concerns that ADF members took loading doses inappropriately, including during the trials.[43] Defence responded that:

> Mefloquine and tafenoquine both have a long half-life and therefore it can take several weeks for sustained protective levels of the drug to be reached. This is a problem when preparing forces for deployment at short notice as it could mean that soldiers are unprotected for periods during the initial deployment period. A loading dose prior to deployment achieves protective levels more quickly… [and] allows any side effects to be identified before deployment and for the medication to be stopped if necessary.[44]

3.22 The product information for Lariam™ (mefloquine) in Australia does not specifically recommend a loading dose, though the product information for New Zealand recommends a loading dose for 'lastminute' travellers.[45] Mefloquine loading doses were found to be tolerable in the United States (US) Marine Corp in the early 1990s.[46] Other militaries experienced malaria outbreaks when mefloquine was used during deployment without a loading dose, including the British in Sierra Leone and the US in Somalia.[47] Professor Dennis Shanks, Director of ADFMIDI, reasoned that if

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39 The new product information for the use of tafenoquine for the prevention of malaria also recommends a loading dose. *Submission 1.1*, pp. 11–12.

40 Dr Peter Stewart, Medical Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 3.

41 Boudreau. E. et al., Tolerability of Prophylactic Lariam® Regimes; Trop. Med. Parasitol. 44(1993) 257-265.

42 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 3.

43 For example, see Ms Anne-Maree Baker, *Proof Committee Hansard*, 5 November 2018, p. 36; Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 41.

44 Defence, *Supplementary submission 1.1*, p. 12.

45 Defence, *Submission 1*, pp. 36–37.

46 Professor Dennis Shanks, Director, ADFMIDI, *Committee Hansard*, 11 October 2018, p. 55. See also Defence, *Supplementary submission 1.1*, p. 12.

47 Professor Shanks, *Committee Hansard*, 11 October 2018, p. 55; Defence, *Supplementary submission 1.1*, p. 12.

the ADF had not provided loading doses it 'would be doing something that we knew had not worked operationally at least twice instead of what we knew was tolerable based on actual testing'.[48]

Period of time taking antimalarial drugs

3.23 The committee heard concerns that some ADF members took antimalarials for too long and negatively affected their health.[49] However, the American Centers for Disease Control and Prevention 'recommends that mefloquine be started two or more weeks before entering a malarious area and does not specify a maximum duration of treatment, judging it to be suitable for long term prevention'.[50] Moreover:

> Mefloquine had been successfully used for long periods in Africa by the US Peace Corps prior to the Timor-Leste studies with no evidence of long term health effects. Long term follow-up of the US Peace Corps, a majority of whom took mefloquine, showed no serious adverse effects attributable to the medication after more than 10 years.[51]

3.24 Also referring to evidence from the Peace Corps, Professor James McCarthy, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute, noted the rate of side effects went down as people took mefloquine for longer.[52] Some people could not tolerate mefloquine so stopped taking it very quickly, however another group were able to take it for a very long time without side effects.[53]

Use of antimalarial drugs outside the trials

3.25 At the time of the trials, mefloquine was registered by the TGA, so personnel could take it if they had issues tolerating doxycycline, as was the case for some submitters.[54] Personnel who were deployed at the time of the tafenoquine prevention trial, but not actually participating in the trial, could choose to take doxycycline or mefloquine.[55] Defence explained that '[t]he exact number of individuals who were prescribed mefloquine during Timor-Leste deployments outside of the studies is unknown as Defence did not have a complete electronic dispensing record until 2001'.[56]

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48 *Committee Hansard*, 11 October 2018, p. 55.

49 See *Proof Committee Hansard*, 5 November 2018, p. 36.

50 Defence, *Submission 1*, pp. 36–37.

51 Defence, *Supplementary submission 1.1*, p. 21.

52 *Committee Hansard*, 11 October 2018, p. 22.

53 *Committee Hansard*, 11 October 2018, p. 22.

54 See, for example, Name withheld, *Submission 48*, p. 1.

55 Defence noted that this was 'to simplify health surveillance activities by aligning dosage requirements with the rest of the group', and Mr Reid also noted that it was to prevent 'an inducement for the soldiers to go into the trial unnecessarily'. Defence, *Supplementary submission 1.1*, p. 9; *Committee Hansard*, 30 August 2018, p. 21.

56 *Supplementary submission 1.1*, p. 9.

3.26 Excluding trial participants, 664 ADF personnel were prescribed mefloquine from 2001 to 20 June 2018.[57] Prescriptions have decreased in recent years:

> …on average 76 members being prescribed the drug each year during 2001–2005, 33 members each year during 2006–2010 and 19 members each year during 2011 to 2015. In the past two years, the figure has been five and two respectively.[58]

Current ADF antimalarial policy

3.27 Defence provided its current policy, which lists doxycycline as the first line antimalarial, Malarone™ second and mefloquine third.[59] The Defence submission indicated that tafenoquine would be considered for use if it was registered by the TGA (as it has been), and a new Defence policy is expected to be released in late 2018.[60]

Details of the antimalarial drug trials

3.28 Defence stated:

> The maximum number of Defence personnel who have taken mefloquine and tafenoquine in the ADFMIDI [ADF Malaria and Infectious Disease Institute] studies, and the number of prescriptions of mefloquine outside of these studies since 2001, is 3,523. It is likely that this is an overestimate as there may be some overlap in these groups.[61]

3.29 This 3,523 comprises a maximum of 1,983 people who took mefloquine and 1,540 who took tafenoquine.[62]

3.30 The following table presents information on the trials, though it 'does not include every single unit that made up the deploying Battalion Group', and the tafenoquine 'eradication and treatment studies included personnel from a large number of units in addition to those listed'.[63]

57 Defence, *Submission 1*, pp. 14, 20.

58 Defence, *Submission 1*, p. 14.

59 *Submission 1*, p. 36, Annex T.

60 *Submission 1*, pp. 2, 36.

61 *Submission 1*, p. 20.

62 Defence, *Submission 1*, Annex E, [p. 149].

63 Defence, *Supplementary submission 1.1*, p. 8.

Table 1: ADF antimalarial studies 1999 to 2002

Trial	Number of participants taking antimalarial	Approximate dates	Location	Personnel involved	Dosages
Tafenoquine eradication[64]	Tafenoquine 1017 (378/639) Primaquine 464	February 1999 to April 2000	Bougainville (1999)/ Timor-Leste (2000)	3 RAR, 5/7 RAR, others	Tafenoquine: over 3 days either: 400mg daily; 200mg twice daily; or in Timor-Leste only, 200mg daily
Tafenoquine prevention[65]	Tafenoquine 492 Mefloquine 162	October 2000 to April 2001	Timor-Leste	1 RAR	Tafenoquine: 200mg daily for 3 days then 200mg weekly Mefloquine: 250mg daily for 3 days then 250mg weekly
Mefloquine prevention[66]	Mefloquine 1157 Doxycycline 388	2001–2002	Timor-Leste	2 RAR and 4 RAR	Mefloquine: 250mg every other day on 3 occasions, then a 250mg weekly dose
Tafenoquine treatment[67]	Tafenoquine 31	2000–2001	Australia	Various	Tafenoquine: 200mg daily for 3 days then 200mg weekly for 8 weeks

Sources: Defence, *Submission 1*, pp. 20–21; *Submission 1.1*, p. 8; papers listed in footnotes to the table.

64 See N Elmes, P Nasveld, S Kitchener, D Kocisko, M Edstein, 'The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific', *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 102, no. 11, November 2008, pp. 1095–101.

65 See P Nasveld, M Edstein, M Reid, L Brennan, I Harris, S Kitchener, P Leggat, P Pickford, C Kerr, C Ohrt, W Prescott et al, 'Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects', *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 2, 2010, pp. 792–8.

66 See S Kitchener, P Nasveld, R Gregory, M Edstein, 'Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor', *Medical Journal of Australia*, vol. 182, no. 4, 2005, pp. 168–171.

67 See S Kitchener, P Nasveld, M Edstein, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', *American Journal of Tropical Medicine and Hygiene*, vol. 76, no. 3, 2007, pp. 494–6.

Reasons for ADF involvement

3.31 Defence indicated that the broad purpose of the trials was to consider the use of alternatives to the standard medications in use at the time, including primaquine and doxycycline.[68] Prior to the trials there were cases of relapsing malaria during deployments, and it was not known whether this was due to compliance problems with primaquine or if the malaria parasite was developing resistance.[69] Moreover, during the 1999 INTERFET operation, 64 cases of malaria were recorded while using doxycycline, and 212 soldiers experienced the onset of malaria after returning to Australia.[70] Defence noted this could have been due to poor compliance or possible resistance to doxycycline, so sought to assess the use of other medications.[71]

3.32 Some submitters suggested the mefloquine prevention trial was unnecessary, as 'studies of long-term mefloquine prophylaxis had by this time already been conducted involving military personnel…providing seemingly ample evidence to adequately inform ADF policy'.[72] Compared to other militaries, 'the ADF has been conservative in its use of mefloquine',[73] and sought to define the safety and tolerability of mefloquine and assess its effectiveness under operational conditions.[74]

Allegations regarding conflicts of interest

3.33 Some submitters claimed there were conflicts of interest during the trials, such as Associate Professor Quinn, who pointed out 'the doctors, the medical officials and the senior ADF members who are managing that deployed cohort are also invested in the development and delivery of a third-party pharmaceutical-funded drug trial'.[75] She suggested the 'close interdependency' between organisations and:

> The implicit pressures on the AMI [Army Malaria Institute] staff carrying out the trial to deliver positive outcomes for these agencies likely biased results an[d] resulted in drug continuation for some participants where withdrawal from treatment was indicated.[76]

3.34 As another example, Mrs Mary Bush told the committee that she perceived the trials involving tafenoquine to be unethical as she alleged participants 'were used as human guinea pigs for the government's own gain, namely money and greed'.[77]

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68 *Supplementary submission 1.1*, p. 6.

69 Defence, *Supplementary submission 1.1*, p. 6.

70 Defence, *Supplementary submission 1.1*, p. 6.

71 *Supplementary submission 1.1*, p. 6.

72 The Quinism Foundation, *Submission 17*, p. 9.

73 Vice Admiral David Johnston AO, *Committee Hansard*, 11 October 2018, p. 45.

74 AQVFA, *Submission 16.3*, Annex 1, [p. 15].

75 *Proof Committee Hansard*, 5 November 2018, p. 40.

76 The Australian Malaria Institute has been renamed the ADF Malaria and Infectious Disease Institute. AQVFA, *Submission 16*, pp. 19, 45–47.

77 *Proof Committee Hansard*, 5 November 2018, p. 11.

3.35 The conduct of the trials has been scrutinised several times. It was reported in 2015 that the chair of the ethics committee that preceded the DDVA HREC reviewed documentation available at the time of the trials and the conduct of the researchers.[78] It determined that Defence and the ethics committee applied appropriately rigorous scientific and ethical evaluation of the trials.[79] The 2016 IGADF report found the trials undertaken from 2000 to 2002 in East Timor involving mefloquine 'were conducted ethically and lawfully'.[80] More details on the IGADF report are included later in this chapter. In 2018, the US Food and Drug Administration (FDA) conducted an audit of Defence's tafenoquine trials, and 'confirmed compliance with the approved protocols and conformity with the Declaration of Helsinki (1996) and International Conference of Harmonisation Guidelines for Good Clinical Practice'.[81] The audit found 'no conclusion of impropriety' and 'no indication that good clinical practice was not followed'.[82] Defence characterised the audit as representing 'a thorough, independent validation of all aspects of the conduct of the studies'.[83]

3.36 Allegations of misconduct were also refuted by pharmaceutical companies and Defence. Organisations such as ADFMIDI, the US Army's Walter Reed Army Institute of Research and Medicines for Malaria Venture (MMV) collaborate, but Defence emphasised it does not have 'direct financial relationships with the drug companies associated with the development of tafenoquine'.[84] Associate Professor Karunajeewa, who was not involved in the trials, stated:

> …AMI and its members are very well-respected as scientists and academics and their contributions to this effort are genuinely very highly valued throughout our small community. We all do our best to co-operatively draw on a wide variety of resources including government, academia, public-private partnerships, non-government organizations and industry…I am not aware of any evidence to support suggestions that clinical trials in Bougainville and Timor Leste were ethically compromised by pecuniary interests or collusion with the pharmaceutical industry.[85]

3.37 In its submission, Defence noted that malaria is more prevalent in poorer countries, so it is difficult for pharmaceutical companies to recoup the development costs of antimalarials.[86] While not directly involved in the trials, the pharmaceutical

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78 The Australian Defence Human Research Ethics Committee (ADHREC), *Annual Report 2015*, Department of Defence, 2016, p. 7.

79 ADHREC, *Annual Report 2015*, Department of Defence, 2016, p. 7.

80 IGADF, *Inquiry report*, 2016, pp. ii–iii.

81 Defence, *Supplementary submission 1.1*, p. 5.

82 The FDA considered 'study 033' (the tafenoquine prevention trial) and 'study 049' (the tafenoquine eradication trial). *Proof Committee Hansard*, 8 November 2018, p. 18.

83 *Supplementary submission 1.1*, p. 5.

84 *Submission 1*, p. 17.

85 *Submission 15*, [p. 12].

86 *Submission 1*, p. 16.

company Roche confirmed that mefloquine represents a very small portion of their business at less than $1 million per year and less than one per cent of turnover.[87] The pharmaceutical company GlaxoSmithKline (GSK), sponsor of some tafenoquine studies, emphasised that its 'aim is to make that drug available in malaria-endemic countries at an affordable price' and reiterated that this 'is not a commercial opportunity for GSK'.[88] Defence also refuted the claim that pharmaceutical companies stand to make millions of dollars from the registration of tafenoquine, pointing out that its global roll out will cost more than an estimated US$100 million, and probably require continued subsidy.[89] The US military 'also continues to invest a great deal of money in tafenoquine because it is required for force health protection'.[90]

3.38 Tafenoquine was not registered for nearly two decades following the trials, a length of time described as 'unusual' by Adjunct Professor John Skerrit, Deputy Secretary, Health Products Regulation, Department of Health.[91] However, GSK explained that it initially worked with the US Army in the early 2000s, and then changed direction to focus on developing a radical cure with MMV, noting 'a 10-year time frame to develop the medicine for that setting is not that unusual'.[92]

Concerns about access to research data

3.39 The AQVFA expressed concerns that data from the tafenoquine prevention trial were provided to 60P without the re-consent of trial participants.[93] 60P responded that its use of de-identified data in regulatory dossiers and for pharmacovigilance reporting was appropriate. The original information and consent form signed by participants informed them that 'data collected as part of the studies would be kept for 75 years'.[94]

3.40 Professor Sandy McFarlane AO, Director, Centre for Traumatic Stress Studies, University of Adelaide, raised the broader issue of how to 'allow access to and use of data collected in Defence and DVA sponsored research programs' to ensure it is used optimally while protecting the privacy of participants.[95]

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87 Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 5.

88 Dr Alison Webster, Head, Global Health Clinical Research and Development, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12.

89 *Supplementary submission 1.1*, p. 18.

90 Defence, *Supplementary submission 1.1*, p. 18.

91 *Proof Committee Hansard*, 11 October 2018, p. 37.

92 Dr Webster, *Proof Committee Hansard*, 8 November 2018, p. 14.

93 60P is also referred to as 60 Degrees Pharmaceuticals LLC. AQVFA, *Submission 16.1*, p. 3.

94 60P, *Supplementary submission 9.1*, p. 2.

95 *Submission 58*, [p. 5].

The consent process during the trials

3.41 This section summarises the trial consent process, including ethics committee approval and the provision of information and choice to prospective participants. In its submission, Defence provided the consent forms and information sheets for most of the trials.[96] Defence also provided the original and amended study protocols relating to the tafenoquine prevention trial (study 033) as well as related documentation in its supplementary submission.[97] The AQVFA provided some documentation related to the mefloquine prevention trial.[98]

3.42 The Australian Defence Medical Ethics Committee (ADMEC) was created in 1988 to be a committee of impartial experts responsible for ensuring trials are 'both ethically permissible and scientifically correct'.[99] It was called the Australian Defence Human Research Ethics Committee (ADHREC) from 2001–2017, and then replaced by DDVA HREC. ADMEC considered research protocols in line with a precursor to the current National Statement, the 1999 *National Statement on Ethical Conduct in Research Involving Humans* (National Guidelines).[100] The provisions pertinent to research involving ADF members are almost directly the same in the 1999 National Guidelines and as the current National Statement.[101] ADMEC reviewed and approved the protocols for the antimalarial trials.[102]

Disclosure of risks and provision of information

3.43 Providing sufficient information to prospective participants involves giving them 'an adequate understanding of the purpose, methods, demands, risks and potential benefits of the research'.[103] Some submitters suggested that though participants were provided with information and signed consent forms, this did not constitute consent because they did not understand the information. Lieutenant General John Caligari AO DSC (Rtd) explained:

> Informed consent for a lot of these soldiers would have been: 'Hey, it's all right for the boss. He thinks it's okay. It's in the army newspaper. It must be okay. Someone's let them on the base to describe it. It must be okay.'…they've probably walked in and the doctor started explaining it to them, and they're not really listening…That's not informed consent, because they're not listening. They don't understand what they're reading.[104]

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96 The forms are for the mefloquine prevention, tafenoquine prevention and tafenoquine eradication trials. See *Submission 1*, Annexes F to H.

97 *Supplementary submission 1.1*, Annex C, [p. 78].

98 *Supplementary submission 16.3*, Annexes 1 and 2.

99 IGADF, *Inquiry report*, p. i.

100 IGADF, *Inquiry report*, p. 7.

101 Ms Barr, *Committee Hansard*, 11 October 2018, p. 13.

102 Defence, *Submission 1*, pp. 22, 25.

103 NHMRC, ARC and Universities Australia, *National Statement*, p. 16.

104 *Committee Hansard*, 31 August 2018, p. 25.

3.44 A veteran described that prior to the tafenoquine prevention trial they were too focused on preparation for deployment to 'fully understand medical terminology used or the drugs that we were being exposed to'.[105] Another veteran told the committee: 'Truthfully, I didn't even read it. The sergeant just gave out a piece of paper and we all just signed it so that we [could] go to Timor'.[106]

Inspector-General of the Australian Defence Force investigation

3.45 The statutory role of IGADF was established to 'provide a means for review and audit of the military justice system independent of the ordinary chain of command'.[107] In 2015, then Major Stuart McCarthy lodged a wide-ranging submission with the IGADF alleging 'unethical, unlawful and negligent use by Defence of the anti-malarial drug mefloquine' during the trials held between 2000 and 2002 involving members deploying to East Timor.[108] He claimed that Defence failed to comply with National Guidelines because members were compelled to participate in one of the trials as a condition of deployment and there was a lack of informed consent in both trials.[109] Major McCarthy's complaint also focused on the purported 'neurotoxic' effects of mefloquine and the claim that the AMI failed to ensure prospective participants were 'informed of the foreseeable likelihood of permanent brain injury with long term or permanent side effects'.[110] Similar allegations were outlined in submissions to this inquiry from Mr McCarthy, the AQVFA, the American Quinism Foundation and some individuals.[111]

3.46 The IGADF concluded that Defence and AMI investigators did not accept the claim that mefloquine caused 'mefloquine neurotoxicity'.[112] As noted above, the IGADF also found that the trials undertaken by the AMI from 2000 to 2002 in East Timor involving mefloquine 'were conducted ethically and lawfully by the AMI, in accordance with the National Guidelines issued by the NHMRC and the TGA'.[113] Details on the provision of information in specific trials are below.

Tafenoquine prevention trial

3.47 This trial compared tafenoquine and mefloquine. The Quinism Foundation, led by Dr Remington Nevin, raised concerns that:

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105 Name withheld, *Submission 67*, p. 1.

106 Mr Warren Goodchild, *Committee Hansard*, 31 August 2018, p. 31.

107 Defence, *Military Justice: Organisations*, http://www.defence.gov.au/mjs/organisations.asp#1 (accessed 2 October 2018).

108 IGADF, *Inquiry report*, pp. 1–2.

109 IGADF, *Inquiry report*, 2.

110 IGADF, *Inquiry report*, p. 24, [original emphasis removed].

111 Mr Stuart McCarthy, *Submission 94*; AQVFA, *Submission 16.3*; Quinism Foundation, *Submission 17*, pp. 5–10.

112 IGADF, *Inquiry report*, p. 49.

113 IGADF, *Inquiry report*, 2016, pp. ii–iii.

> …guidance in the then-current Australian mefloquine Patient Information to stop taking the drug and to 'tell your doctor immediately or go to casualty at your nearest hospital' for 'change in mood, for example, depression, restlessness, confusion, feeling anxious or nervous' do not appear to have been communicated to subjects.[114]

3.48 However, the consent form and information sheet stated:

> Should you experience any medical problems, including suspected side effects to the study drugs, you should report these promptly to your Company medic, RAP or study investigator. If you want any further information on the study, please contact the study investigator…[115]

3.49 Fourteen witnesses were interviewed as part of the IGADF inquiry, and while most of them 'had a limited and vague memory of the informed consent process', almost all accepted that 'the medical briefings dealt with the potential side effects of both drugs and that the trial was voluntary'.[116] The IGADF reported that participants:

> …undertook a comprehensive three phase medical briefing process culminating in a witnessed consent form being signed before a medical officer. This process ensured that participants were aware of the potential side effects of both drugs and that the trial was a voluntary trial, without detriment to deployment, and they could withdraw at any time.[117]

3.50 The IGADF was 'satisfied the trial participants were appropriately informed by the medical investigators of the potential side effects of both tafenoquine and mefloquine, and understood that participation in the trial was voluntary without detriment to deployment or future career'.[118] Lieutenant General Caligari (Rtd) said participants were:

> …individually briefed by a doctor, and a witness with the doctor, and signed the documents after they were asked, 'Do you believe you understand enough about the trial?' I was very satisfied with the way the AMI conducted the introduction of everyone into the trial...There were also group sessions that were held which I made them all attend. They received briefings on whiteboards and PowerPoint presentations on what this drug was all about, what the purpose of the trial was and what the possible implications of it were….every soldier signed in front of a doctor, or at least the RAP sergeant, with a witness.[119]

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114 *Submission 17*, p. 9.

115 Defence, *Submission 1*, Annex G, [p. 159].

116 IGADF, *Inquiry report*, p. iii.

117 IGADF, *Inquiry report*, p. iii.

118 IGADF, *Inquiry report*, p. 49.

119 *Committee Hansard*, 31 August 2018, pp. 21, 23.

Mefloquine prevention trial

3.51 This trial compared mefloquine and doxycycline. Mefloquine had already been approved and registered in Australia at the time of the trial.[120] On direction from the ethics committee of the time, the information and consent form for the trial were amended to 'clearly outline in quantitative terms the side effects of the medication'.[121] The information on mefloquine's potential side effects provided in the 4 RAR and 2 RAR trial medical briefings and consent form was consistent with the detailed 1998 Lariam (mefloquine) product information.[122]

3.52 The IGADF judged that this 'provided sufficient relevant information in a form comprehensible to participants, to allow them to make an informed decision whether or not to participate in the trial'.[123] The IGADF inquiry found:

> Participants in the 4 RAR and 2 RAR mefloquine anti-malarial drug trials received a comprehensive medical briefing, during which they were informed of the side effects of mefloquine, that the trial was completely voluntary, and non-participation would have no effect on deployment or career. These aspects were reinforced at individual doctor/participant consultations when mefloquine was prescribed to the soldiers taking part in the trial. After the loading dose was administered in Australia and prior to deployment, the soldier had a further opportunity to discuss any side effects with a medical officer and to withdraw from the trial.[124]

3.53 Some submitters recounted memories of receiving briefings about the trial.[125]

Tafenoquine eradication trial

3.54 This trial compared tafenoquine and primaquine. Mr McCarthy recalled receiving a briefing from trial investigator Colonel Peter Nasveld, but noted:

> …In Bougainville there was no internet. We literally wrote letters home. We had a satellite phone there. We were given one two-minute phone call home per week. So there was absolutely no way to check the veracity of the information we were told.[126]

3.55 Mr Stuart McCarthy and Mr Brian McCarthy also expressed concerns that they had not viewed evidence that the TGA approved the export of tafenoquine to East

120 IGADF, *Inquiry report*, 2016, p. vi.

121 The protocol appears to have been amended during 2001. AQVFA, *Submission 16.3*, pp. 4, 121–122.

122 This was more detailed than the 1998 Lariam consumer medicine information normally provided to patients on prescription. IGADF, *Inquiry report*, 2016, p. vi.

123 IGADF, *Inquiry report*, 2016, p. vi.

124 IGADF, *Inquiry report*, 2016, p. vi.

125 See, for example, name withheld, *Submission 76*, p. 3.

126 Mr Stuart McCarthy, *Committee Hansard*, 30 August 2018, p. 6.

Timor for use by 3 RAR participants in the tafenoquine eradication trial.[127] Defence reiterated that tafenoquine 'was administered in accordance with ADMEC approved study protocols and participation was voluntary'.[128] It stated:

> These personnel were briefed about the study, given a written information sheet and the opportunity to ask questions. Those who chose to participate then signed the study consent form and were provided a copy. The consent form included information on their right to withdraw from the study at any time without any consequences. Those who chose not to participate received the standard primaquine eradication course.[129]

3.56 A participant from 3 RAR recalled being briefed, but stated: '[d]uring the enrolment in this clinical trial I was not examined by a doctor'.[130] The study requirement was for 'all individuals to be briefed and consented by a doctor', but perhaps not physically examined as the participant appeared to expect.[131] The committee understands that ADF members underwent pre-deployment medicals as part of the usual preparation process external to the trials.[132]

Tafenoquine treatment trial

3.57 Defence noted giving tafenoquine to 31 members with relapsing malaria 'was not a study per se but a quality assurance activity'.[133] Tafenoquine was not registered at the time of the trials, so TGA approval was required to import the medication under the Special Access Scheme.[134] An academic paper stated:

> The proposal to conduct this treatment trial was reviewed and approved by the [ADHREC], and each individual patient signed an informed consent and information sheet and their treatment was approved by the Australian Therapeutic Goods under the auspices of the Therapeutics Goods Act (1989), Section 19(1).[135]

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127 Mr Brian McCarthy, *Supplementary submission 73.2*, pp. 7–8; Mr Stuart McCarthy, *Submission 94*, pp. 9–10.

128 *Submission 1*, p. 25.

129 Annex G of the Defence submission includes four versions of the information sheet and consent form. Defence, 'Tafenoquine Eradication and Treatment Trials', http://www.defence.gov.au/Health/HealthPortal/Malaria/AMI_research/tafenoquine-trials/eradication-treatment-trials.asp (accessed 8 October 2018).

130 Name withheld, *Submission 59*, [p. 1].

131 Defence, *Supplementary submission 1.1*, p. 12.

132 Defence, *Supplementary submission 1.1*, p. 29.

133 *Submission 1*, p. 24.

134 IGADF, *Inquiry report*, p. 9; Defence, *Submission 1*, p. 25. The TGA manages the Special Access Scheme in recognition that there are circumstances where patients need access to unregistered therapeutic goods. See TGA, 'Special Access Scheme' https://www.tga.gov.au/form/special-access-scheme (accessed 24 July 2018).

135 Kitchener et al, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', p. 494.

3.58 Defence reiterated that participation was 'voluntary and those who agreed to take tafenoquine to treat their relapsing malaria provided consent'.[136]

Voluntary participation

3.59 There are two conditions for consent: the provision of sufficient information and voluntary choice to prospective participants. Consent must be able to be withdrawn even once the trial has started, and prospective participants should be informed of the consequences of this as part of the consent process.[137] The National Statement explains that someone 'declining to participate in, or deciding to withdraw from, research should not suffer any negative consequences'.[138]

3.60 The committee heard concerns that the unequal relationships within the ADF prevented members fully exercising their right to choose whether or not to participate in the trials. The following extract from a submission exemplifies these issues:

> I was 19 years old, have been in the army for approx 7–8 months at this stage, new to the battalion and would be deploying overseas in approx 2 month's time. Who am I to be questioning anything we are taught, trained or advised of especially in an organisation like the Australian Defence Force. From the moment you get off that bus at Kapooka for basic training you now or soon learn very quickly to shut your mouth, do what you are told and don't ask questions.[139]

3.61 The wife of a veteran reiterated that the military 'culture doesn't allow them [soldiers] to say no'.[140]

3.62 Some submitters suggested even though members signed consent forms, this could not be understood to be voluntary consent because they felt pressured to participate. Mr Kel Ryan, National President of the Defence Force Welfare Association, told the committee 'I suppose they've consented, and I suppose they've agreed with it—they've been informed—but it might be based on a degree of peer pressure'.[141] Mr Mark Armstrong, a veteran who did not participate in the trials, stated:

> Nothing is consensual in the military. Once you sign, if you're going to be a good soldier you say yes. You don't get a choice. If you do, you get hammered…It's a team and you don't want to let that team down.[142]

3.63 Lieutenant General Caligari (Rtd) shared his view that:

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136 Defence, *Submission 1*, p. 25.

137 NHMRC, ARC and Universities Australia, *National Statement*, p. 18.

138 *National Statement*, p. 69.

139 Confidential, *Submission 103*, p. 1.

140 *Committee Hansard*, 30 August 2018, p. 15.

141 *Committee Hansard*, 30 August 2018, p. 29.

142 *Committee Hansard*, 30 August 2018, p. 11. See also Mr Eveille, Returned and Services League of Australia, *Committee Hansard*, 11 October 2018, p. 20.

> I don't think there is any such thing as informed consent in the military. We do things because we are ordered to do things; we don't have the opportunity to say yes or no to some things; we shouldn't have a say in anything….People signed a form and that is what was considered by the trial conductors as informed consent—which was a requirement of the human research and ethics committee.[143]

3.64 In contrast, Vice Admiral Johnston stated:

> My view is that informed consent is available, and important, for military people…on the general comment by General Caligari that it's impossible to have informed consent: we exercise informed consent over a range of our career choices, not just limited to our participation in medical practice.[144]

3.65 He conceded 'these people's recollections now are such that they don't believe they were given informed consent' and 'that's very concerning'.[145] The IGADF found:

> In compliance with NHMRC guidelines, participants in the 2000 to 2002 anti-malarial drug trials conducted by AMI were required to voluntarily confirm their willingness to participate in the trial, that is, exercise a voluntary choice, after having been informed at their level of comprehension of relevant aspects of the trial including the risks and discomforts (side effects) associated with taking the drugs. There were not to be any adverse consequences for failing to participate in the trial.[146]

3.66 Details on the voluntary nature of consent in specific trials are noted below.

Tafenoquine prevention trial

3.67 Principal investigator Colonel Nasveld was responsible for obtaining informed consent from participants and 'was personally present for all of it'.[147] He assured the committee that the consent process:

> …was done according to the best practice and in fact at a level that probably had greater rigour than that generally experienced in the civilian community…they were consented in pairs, at matched ranks, was so there could be no suggestion that there was coercion from a senior person because he said yes and a junior person still had doubt. That briefing period, that consenting period, ran over several weeks. The implication that it was done on the spur of the moment is incorrect…I understand that many, many years later the recollection of that 10 or 20 minutes while you're preparing to go on your first deployment may not flag as strongly as it does with those who have to actually deliver the consenting process. I am

143 *Committee Hansard*, 31 August 2018, p. 20.

144 *Committee Hansard*, 11 October 2018, p. 47.

145 *Committee Hansard*, 11 October 2018, p. 47.

146 IGADF, *Inquiry report*, 2016, p. iii.

147 *Committee Hansard*, 11 October 2018, p. 48.

> extremely comfortable—as was the FDA, the TGA and our internal audits by the ethics committee—in the activities undertaken.[148]

3.68 He explained the regimental medical officer firstly provided an outline of the trial as part of a briefing to companies about general health risks.[149] In smaller groups, members were given information and consent forms and briefed by medical officers as part of their general health screening, which included the opportunity to ask questions about the trial.[150] Members did not return their signed forms until at least two days later, to enable them to consider their choice and consult with friends and family.[151]

3.69 Defence has a duty of care to ensure its members are protected from malaria when they deploy to malarious areas.[152] Colonel Nasveld acknowledged that ADF members would not deploy in such situations without taking an antimalarial, but stressed that this is 'not the same as saying, 'You must be on this study'.'[153] The IGADF investigated the allegation that the Commanding Officer (CO), then Lieutenant Colonel Caligari, told 1 RAR troops they would not deploy if they did not participate in the trial.[154] This claim was made in then Major McCarthy's submission to the IGADF, and in information provided to the committee's inquiry.[155] Lieutenant General Caligari (Rtd) denied the allegation.[156]

3.70 The IGADF inquiry found witnesses' 'overall memory of events surrounding the anti-malarial drug trial, conducted during a busy pre-deployment 16 years ago is generally poor and lacking in detail'.[157] The IGADF concluded:

> There is differing but credible evidence provided by the six witnesses identified by MAJ McCarthy, and the former command group officers and LTGEN Caligari concerning voluntary participation in the trial. The sufficiency and quality of the evidence does not satisfy the required standard of proof to make an adverse finding that the CO used the alleged words (or a similar threat or direction) to the effect that participation in the trial was required in order to deploy to East Timor.[158]

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148 *Committee Hansard*, 11 October 2018, p. 48. See also Mr Reid, *Submission 71*, p. 12.

149 *Committee Hansard*, 11 October 2018, p. 49.

150 *Committee Hansard*, 11 October 2018, p. 49.

151 *Committee Hansard*, 11 October 2018, p. 50.

152 Defence, *Supplementary submission 1.1*, p. 16.

153 *Committee Hansard*, 11 October 2018, p. 50.

154 IGADF, *Inquiry report*, 2016, p. iii.

155 See, for example, Mr Brock, *Committee Hansard*, 31 August 2018, p. 9; Mr Chris Ellicott, *Submission 105*, p. 1; Mr Todd Connors, *Submission 99*, [p. 1]; Mr Glen Norton, *Submission 80*, [p. 1].

156 IGADF, *Inquiry report*, p. 50; LTGEN Caligari, *Committee Hansard*, 31 August 2018, p. 25.

157 IGADF, *Inquiry report*, p. 50.

158 IGADF, *Inquiry report*, p. 56.

3.71 ADF members did not have to participate in the trial, and could deploy while taking other antimalarial drugs such as doxycycline. Colonel Nasveld noted:

> …we had people who would come up and say, 'Listen, I'm not comfortable with being part of the study.' They all knew they had an option of not being there or commencing on another antimalarial. They even had a choice of taking any of the antimalarials that were available, having had a discussion on what the side-effect profiles of those were.[159]

3.72 The IGADF inquiry heard that over 400 deployed members of the battalion group did not participate in the trial and were taking doxycycline.[160] It was noted that such large numbers of non-participants was not consistent with the CO threatening that those who refused to participate would not deploy.[161] The AQVFA suggested that the majority of these would have been excluded from the trial for medical or administrative reasons, because they were due to be posted in or out of 1 RAR partway through the deployment, or because they were not initially members of 1 RAR.[162] Colonel Nasveld noted that, in addition to these reasons for not participating, some prospective participants 'basically just said no'.[163] According to trial records, '95 personnel were recorded as being unwilling or unable to enrol and another 24 were excluded as they were found unsuitable on screening'.[164] Defence stated that '[n]o evidence has been presented that anyone was stopped from deploying because they refused to participate'.[165] The IGADF report was criticised by veterans and commentators who did not accept the findings.[166]

Mefloquine prevention trial

3.73 The IGADF noted 'investigators went to some lengths to ensure voluntary participation', including offering soldiers opportunities to withdraw.[167] This 'may not have impacted on the soldiers' decision to automatically participate', as they perceived the trial as just 'one of the many pre-deployment matters that had to be completed in order to deploy'.[168] For example, Mr Fleming recalled the trial was not:

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159 *Committee Hansard*, 11 October 2018, p. 49. See also Mr Reid, *Committee Hansard*, 30 August 2018, p. 21.

160 IGADF, *Inquiry report*, pp. 37–38, 51. See also Defence, *Submission 1*, p. 23.

161 IGADF, *Inquiry report*, p. 51.

162 AQVFA, *Supplementary submission 16.6*, pp. 3–4.

163 *Committee Hansard*, 11 October 2018, p. 50.

164 Defence, *Supplementary submission 1.1*, p. 11.

165 *Supplementary submission 1.1*, p. 11.

166 For example, Mr Brian McCarthy, *Submission 73*, pp. 6–8, Mr Stuart McCarthy, *Committee Hansard*, 30 August 2018, pp. 3–4; Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, pp. 39–40.

167 IGADF, *Inquiry report*, pp. 70–71.

168 IGADF, *Inquiry report*, pp. 71, 73.

> …high on my priority list with fitness and preparation for deployment taking higher priorities. It very much sounded like it made sense at the time, having to take one tablet a week instead of daily and in general as soldiers we trusted that our medical support had our best interest in mind.[169]

3.74 Nevertheless, the IGADF concluded members 'were not compelled or coerced by command to participate in the 4 RAR and 2 RAR anti-malarial drug trials and to take mefloquine'.[170]

Tafenoquine eradication and treatment trials

3.75 The committee did not receive as much evidence on voluntary consent for these trials, but it appears that consent was provided.[171] For instance, Major Phillip Chapman (Rtd) described his experience of the tafenoquine eradication trial:

> …I was a volunteer for this trial and volunteered because the benefits of taking Tafenoquine as a post-deployment eradication were 'sold' to us, at the briefing for the trial (three days pre-departure for Tafenoquine), as the being a far better option than the arduous task of taking the alternative 'standard' 14 day post-departure eradication program.[172]

Screening processes

3.76 Colonel Nasveld explained that the 'screening process was different for each of the trials'.[173] Generally, ADF members could be excluded from the trials by choice or for reasons including pregnancy, allergic reactions, enzyme G6PD deficiencies or previous experiences of mental illness such as serious depression.[174] The committee heard some concerns that the mental health of prospective participants was not checked prior to them consenting to participate. For example, Ms Anne-Maree Baker noted '[w]e had no specific psych testing prior to deployment as part of this trial'.[175] Defence:

> …uncovered a small number of cases of other individuals who were included in the mefloquine studies despite having a history of mental health issues…Defence acknowledged the error, apologised, and offered to provide assistance to help access support services and engage with DVA.[176]

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169 *Submission 72*, [p. 1].

170 IGADF, *Inquiry report*, 2016, p. viii.

171 See Defence, *Submission 1*, Annex H, [pp. 161–179]; Kitchener et al, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', p. 494.

172 *Submission 87*, [p. 1].

173 *Committee Hansard*, 11 October 2018, p. 53.

174 See the information and consent forms for details on specific trials. Defence, *Submission 1*, *Submission 1*, Annexes F to H.

175 *Proof Committee Hansard*, 5 November 2018, p. 36.

176 Defence, *Submission 1*, p. 40.

3.77 For example, AVM Smart wrote to apologise to a veteran whose previous history of depression was not identified prior to participating in a trial, partly due to the reliance on paper records.[177] It was noted that such a situation would 'not happen today as Defence introduced an electronic Health System in 2014 making it easier for health providers to access documentation'.[178]

Tafenoquine and mefloquine prevention trials

3.78 Colonel Nasveld explained the tafenoquine prevention trial screening entailed:

> …going into the health records and reviewing what was written inside them. That's not to say that with doctors handwriting we might not have missed one or two, but certainly that was the focus. That was also secondarily checked by an audit team from USAMMDA, the United States Army Medical Materiel Development Activity. They had independent people come over and confirm that we were fairly well on the mark.[179]

3.79 Mr Fleming recounted his experience prior to participating in the mefloquine prevention trial: 'There was certainly no review of suitability to take the medication, no examination by a doctor or medic etc other than signing the waiver form and self-assessing your own suitability'.[180] However, Defence stated that each participant of that trial 'was medically assessed prior to starting the study, during deployment and before return to Australia'.[181] This discrepancy may be due to the expectation that prospective participants would have undergone a physical medical examination specifically to assess their suitability for the trial, compared to the approach described by Colonel Nasveld above.

Response to adverse events

3.80 The Defence submission included a summary of the adverse events experienced by ADF members while participating in the trials.[182] Defence defined an adverse event as 'an untoward occurrence associated with (but not necessarily caused by) a medication'.[183] These included events that had not been causally linked to the medication, for example, trial records 'include adverse events such as 'spider bites' which are obviously not related to the use of medication'.[184] Colonel Nasveld stressed that the details of any adverse events were recorded, including when they started and ended.[185] Members could report:

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177 *Committee Hansard*, 11 October 2018, p. 53.

178 Defence, *Supplementary submission 1.1*, p. 29; *Committee Hansard*, 11 October 2018, p. 53.

179 *Committee Hansard*, 11 October 2018, p. 53.

180 *Submission 72*, [p. 2].

181 *Submission 1*, p. 23.

182 *Submission 1*, Annex V, Adverse Event Reporting in AMI Studies 1999–2002.

183 *Submission 1*, p. 38.

184 Defence, *Submission 1*, p. 38.

185 *Committee Hansard*, 11 October 2018, p. 56.

> …to the study team doctors through the structured interviews conducted at programmed intervals during the study, or by reporting to their supporting health element. If reported by the former, individuals were referred to the supporting health element…If symptoms were severe and thought to be associated with the antimalarial medication being taken, or if requested by the individual, the medication was ceased and an alternative provided.[186]

3.81 Adverse events reported by participants were recorded in both the study Case Record Form to gather data for the trial, and the health treatment data forms for individuals, which were later filed in individuals' medical documents.[187] Some submitters agreed that adverse events were documented in their records, such as Major Chapman (Rtd) and Mr King.[188]

3.82 Some submitters claimed that adverse events were systematically underreported during the trials. The committee heard various reasons for this, including differing perceptions or memories of the events. For instance, Ms Baker indicated that while the adverse events she experienced during the trial were documented as 'mild', she felt that they should have been recorded as more serious.[189] Another potential reason for the claimed underreporting was that participants were reluctant to report their experiences. Mr Ben Whiley explained:

> The minute you show any kind of weakness or anything, there's the mental stigma and your career is over. So many guys have had to hide what was going on to continue with their careers.[190]

3.83 Mr Michael Kruizinga suggested that participants were unlikely to disclose issues when they were about to deploy, go on leave or go home:

> When the soldiers hit the ground back in Townsville, the psych comes up to them and says, 'How was the deployment?' They say, 'Great,' because they are just about to go on post-deployment leave…I think these psych sessions were specifically designed to receive the answers that they got.[191]

3.84 Dr Nevin posited that confusion could also cause underreporting:

> …the user will confuse or misattribute side effects from the drug to the stresses of travel, to the effects of crossing time zones and to the effects of stress on deployment…Because of the tendency to misattribute adverse effects from mefloquine to the environment, it's inherently unsafe to use mefloquine and, I believe, tafenoquine, in a military environment.[192]

3.85 Mr Kruizinga made a similar point:

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186 Defence, *Supplementary submission 1.1*, p. 13.

187 Defence, *Supplementary submission 1.1*, p. 13.

188 *Proof Committee Hansard*, 5 November 2018, p. 37.

189 *Proof Committee Hansard*, 5 November 2018, p. 37.

190 *Committee Hansard*, 30 August 2018, p. 32.

191 *Proof Committee Hansard*, 5 November 2018, p. 5.

192 *Committee Hansard*, 11 October 2018, p. 5.

> Are there negative side effects? Yes. But does the soldier equate them with the drugs that they're taking when the doctor, who tells them that they're going to be taking these drugs, says, 'This drug is safe'? No, the soldier doesn't. When the psych says, 'Was there anything wrong?' they say, 'No, there's nothing wrong at all,' because then the soldier's thinking: 'Maybe it's all in my head. Maybe it's because I've been deployed. This is the first time I deployed. Maybe it's negative side effects. Maybe I've got PTSD.[193]

3.86 A few submitters alleged that the trial investigators themselves underreported adverse events. Dr Nevin compared the reports of psychiatric symptoms including abnormal dreams and insomnia in the trials to those indicated in the most recent meta-analysis of published data, and found rates of reported adverse events for mefloquine during the tafenoquine prevention trial were significantly lower than those reported in the meta-analysis.[194] He alleged this represented 'strong and compelling evidence that adverse drug reactions to mefloquine and tafenoquine, particularly neuropsychiatric adverse reactions, were significantly underreported among ADF personnel by the [AMI]'.[195] The AQVFA also made a range of allegations of systematic underreporting of adverse events by researchers.[196] For example, it raised concerns that not all instances of adverse events identified in the tafenoquine prevention trial were reported to the TGA separately.[197] However, as summarised in the next section, the committee heard that this was because there was no clinical reason to do so as it would not change the course of the follow up for participants, rather than due to clinical malpractice.[198]

3.87 When asked broadly about allegations of underreporting of adverse events by researchers, Professor Shanks, responded:

> It's not true. You can't do that and get your drug registered. The reporting of adverse events is quite detailed, and you don't know what you're going to get till the end. These clinical research forms are filled out as you go, and you report what you find. What that basically says is that we've been conducting fraudulent trials. We reject that assertion and say that the FDA and the TGA also assert that our trials were valid.[199]

3.88 Other witnesses including Mr Reid reiterated that there was no 'underreporting of adverse events during ADF studies; and these studies were audited

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193 *Proof Committee Hansard*, 5 November 2018, p. 5.

194 The Quinism Foundation, *Submission 17*, p. 10. Dr Nevin identified the following meta-analysis: M Tickell-Painter, N Maayan, R Saunders, C Pace, D Sinclair, 'Mefloquine for preventing malaria during travel to endemic areas', Cochrane Database of Systematic Reviews, 2017(10):CD006491.

195 The Quinism Foundation, *Submission 17*, p. 10.

196 *Submission 16*, pp. 18–24; *Supplementary submission 16.1*, pp. 5–10.

197 *Submission 16*, p. 21.

198 Mr Reid, *Supplementary submission 71.3*, p. 3.

199 *Committee Hansard*, 11 October 2018, p. 58. As noted above, the FDA audited the tafenoquine prevention and eradication trials.

by both the TGA and the FDA, including the consenting process'.[200] He noted the tafenoquine prevention trial involved a high rate of adverse reporting when compared to other tafenoquine studies.[201] Details on responses to adverse events in specific trials are summarised below.

Tafenoquine prevention trial

3.89 Some participants in this trial stopped taking the trial medication in response to adverse events.[202] For instance, a corporal who reported an adverse event to Mr Reid saw a psychologist, was put on anti-depressive treatment and was taken off the study drugs.[203] Defence summarised the adverse events during the trial as follows:

> The most common side effects of the tafenoquine prevention study were nausea, vertigo, diarrhoea, abdominal pain, abnormal dreaming and somnolence (drowsiness). 18 (4%) severe adverse events were recorded in the prevention study. These were not all necessarily drug related; for example three were injuries and six were gastroenteritis. No major side effects were observed in the eradication study and no severe neuropsychiatric adverse events were observed in any individuals taking tafenoquine in Defence.[204]

Vortex keratopathy

3.90 Some participants taking tafenoquine experienced benign, reversible 'changes on the surface of the eye (cornea) called vortex keratopathy'.[205] This did not affect participants' vision:

> …and would probably not have been found if the additional eye examination had not occurred. This reflects the high level of care afforded to the participants of the studies.[206]

3.91 The committee heard concerns that this finding was underreported, as only the first five cases were reported to ADHREC, TGA and the US Army Human Subject Research Review Board (HSRRB), rather than each of the 69 individual cases identified.[207] The trial study protocol required that:

> The [Ethics Review Committee] ERC/[Institutional Review Board] IRB must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring

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200 *Committee Hansard*, 30 August 2018, p. 19.

201 Mr Reid, *Supplementary submission 71.3*, pp. 5–6.

202 LTGEN Caligari, *Committee Hansard*, 31 August 2018, p. 22.

203 Mr Reid, *Committee Hansard*, 30 August 2018, p. 20.

204 *Submission 1*, p. 41.

205 Defence, *Submission 1*, p. 17; *Supplementary submission 1.1*, p. 10. See also GSK *Submission 8*, p. 4; GSK, *Supplementary submission 8.1*, p. 2.

206 Defence, *Supplementary submission 1.1*, p. 10.

207 AQVFA, *Submission 16*, p. 21; Mr Todd Connors, *Proof Committee Hansard*, 5 November 2018, p. 18.

> during the study which are likely to affect the safety of subjects or the conduct of the study'.[208]

3.92 However, Mr Reid explained that the corneal deposits did not constitute a Serious Adverse Event as they were 'asymptomatic findings'.[209] He added that a safety report was submitted to the US FDA and provided to the TGA. He emphasised that '[t]here was no clinical reason to submit all 69 reports to ADHREC initially as this did not change the course of the individual follow-up actions with the ADHREC, US Army HSRRB, US FDA and TGA for all subjects for this unexpected finding'.[210]

3.93 The study records of each of the 69 participants who were found to have experienced the corneal deposits were updated to include the findings.[211] At the direction of ADHREC, the follow up was extended from 6 to 12 months.[212] Defence noted that the 'volunteers were subsequently followed up by an ophthalmologist until the changes had fully resolved and all resolved within six months of return to Australia'.[213] Participants were also sent a letter with information on the vortex keratopathy.[214]

Tafenoquine treatment trial

3.94 Treatment was terminated early in four patients due to the finding of vortex keratopathy in the tafenoquine prevention trial.[215] However, no adverse events were reported during the treatment trial, and the medication was well tolerated.[216]

Mefloquine prevention trial

3.95 Participants 'who did not report side effects were still questioned about symptoms', and some received routine blood tests to check that there were no problems.[217] Participants experiencing significant adverse side effects:

> …were examined by medical and nursing officers, the medication was ceased, and the findings recorded while in Timor-Leste. 75 individuals (6.5%) were unable to tolerate the specific antimalarial they were assigned and had to be switched to an alternative…[218]

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208 Mr Reid, *Supplementary submission 71.5*, p. 3, (emphasis added).

209 *Supplementary submission 71.3*, p. 2.

210 *Supplementary submission 71.3*, p. 3. See also GSK, *Supplementary submission* 8.1, p. 2.

211 Defence, *Submission 1*, p. 38; Mr Reid, *Supplementary submission 71.3*, p. 3.

212 Mr Reid, *Supplementary submission 71.3*, p. 3.

213 Defence, *Supplementary submission 1.1*, p. 10.

214 A draft copy of the letter sent to participants with information on vortex keratopathy was included in the following submissions: Defence, *Submission 1*, Annex I, [pp. 180–181]; Name withheld, *Submission 47*, Annex B.

215 Defence, *Submission 1*, pp. 26, 38.

216 Defence, *Submission 1*, p. 26.

217 Defence, *Submission 1*, p. 23.

218 Defence, *Submission 1*, p. 23.

3.96 Defence stated that:

> 57%...of soldiers using mefloquine reported at least one adverse event, compared with 56% using doxycycline. The most commonly reported adverse effects of both drugs were sleep disturbance, headache, tiredness and nausea. There were three serious neuropsychiatric events reported in people taking mefloquine. Two of these individuals had undisclosed medical conditions that would have prevented the prescription of mefloquine if they had been known to medical staff.[219]

3.97 Defence 'has only identified two instances in which members may have had long term, continuing neuropsychiatric side effects after ceasing mefloquine, and no cases among those who took tafenoquine'.[220] Defence noted that it does not have details on the ongoing health of individuals once they leave the ADF.[221]

3.98 The IGADF investigation found that the:

> …medical support provided to the participants before, during and following the [mefloquine and tafenoquine prevention trials] was appropriate. There is no evidence any medical issue at the time was not followed up with appropriate and proper medical care.[222]

Follow up with trial participants

3.99 The AQVFA noted those who stopped participating in the trials early 'appear to have experienced little or no follow-up from the study team'.[223] Colonel Nasveld explained that some who withdrew 'would not have been in location in East Timor to go through the exact rigorous follow-up'.[224] A submitter from 4 RAR whose file was marked 'lost to follow up' stated:

> Due to my early return to Australia at no time did I have any contact from AMI staff in regards to the trial, I had received no debrief in regards to the trial…AMI had neglected in its duty of care to follow up on me...[225]

3.100 AVM Smart indicated that those who withdrew due to illness 'wouldn't have been followed up for the study purposes per se through the normal means', but they would have been 'followed up in terms of the most appropriate medical treatment'.[226]

3.101 In addition, the committee heard varying perspectives on the adequacy of follow up with participants who completed the trials. Defence described participants

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219 *Submission 1*, p. 23.

220 Defence, *Submission 1*, p. 41.

221 *Submission 1*, p. 41.

222 IGADF, *Inquiry report*, p. ii.

223 *Supplementary submission 16.3*, p. 5.

224 *Committee Hansard*, 11 October 2018, p. 54.

225 Name withheld, *Submission 76*, pp. 4, 7–8.

226 *Committee Hansard*, 11 October 2018, p. 54.

receiving 'intense monitoring and health support' during and after the trials, more regular health reviews and blood tests.[227] After the trials, participants:

> …were followed up for six to 12 months from the end of the studies, which was considered enough time for late onset side effects to present. Participants were also given a study card that advised them and their medical practitioner of what to do and who to contact if they were to develop fever during or in the six months after the study.[228]

3.102 While many submitters recalled experiencing something similar to Defence's description, they did not perceive this to be sufficient. For example, Mr Colin Brock reflected that the study card 'was the only thing we received ever, in 18 years, from them'.[229] Details on the follow up for specific trials are outlined below.

Tafenoquine prevention trial

3.103 Mr Wayne Karakyriacos recalled undergoing tests, providing blood samples and speaking with medics at the end of his deployment.[230] However, he viewed this as insufficient to address his ongoing challenges during subsequent years, stating: 'All that time I was untreated. I not once had Defence approach me or the AMI approach me to follow up to see how I was going. Not once did they come back'.[231]

3.104 Defence conveyed a different view of the adequacy of the follow up, noting that 'personnel were monitored closely during the study and for six months afterwards'.[232] Colonel Nasveld insisted the 'follow-up was conducted according to the protocol, and that's well documented in the case record forms for all the participants' apart from those who withdrew from the trial early.[233] The FDA audit only made a minor finding relating to the final telephone follow-up of the trial. Some participants were followed up two months late, however:

> The variance demonstrated the diligence of researchers in continuing to conduct telephone follow-up until all study participants could be contacted, even when outside the stated time limits of the protocol. It was acknowledged that this was indicative of the study team personnel doing all possible to ensure the ongoing welfare of the study participants.[234]

3.105 The committee understands that all participants in the trial received letters informing them that they had taken mefloquine, though 492 had taken tafenoquine.

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227 *Submission 1*, pp. 27–28.

228 Defence, *Submission 1*, p. 28.

229 *Committee Hansard*, 31 August 2018, pp. 16–17.

230 *Committee Hansard*, 31 August 2018, p. 10.

231 *Committee Hansard*, 31 August 2018, pp. 10–11.

232 *Submission 1*, p. 25.

233 *Committee Hansard*, 11 October 2018, p. 54.

234 Defence, *Supplementary submission 1.1*, p. 5.

This was corrected with subsequent correspondence.[235] As noted above, tafenoquine recipients were advised that some participants had developed vortex keratopathy.[236]

3.106 AVM Smart explained to the committee that:

> …as well as the actual specific follow-up that we did as part of the study and interactions during the study we had ongoing health surveillance activities happening. That included post-deployment psychological screening…conducted with proper psychological screening instruments. It is actually designed to pick up things like PTSD and other stressors.[237]

The '100 Club'

3.107 Approximately 100 participants were selected for additional testing and assessment before, during and after deployment.[238] This included 'eye and lung function tests that were done before (within three weeks) and after (within four weeks) deployment, and the taking of an additional 20mls of blood'.[239] Several submitters described this testing, such as Mr Aaron King, who recalled having blood, lung and eye tests.[240] A few submitters suggested that they were also anticipating other medical checks that did not occur.[241] For example, Mr Brock underwent tests after six or seven months on deployment, and recalled being 'told there would be follow-up tests in six months and in 12 months, but these never eventuated'.[242]

Mefloquine prevention and tafenoquine eradication trials

3.108 Submitters differed in their view of what adequate follow up entails. For example, Defence indicated that follow up, including the provision of an information card, was provided over several months following return to Australia.[243] However, Mr Fleming indicated that this was insufficient, recalling that a review was not undertaken following the mefloquine trial (other than a one-page survey), and noting that he was never spoken to by a doctor or a trial facilitator about his experience.[244] Similarly, Major Chapman (Rtd) described the follow up from the tafenoquine eradication trial as 'pretty poor', and stated:

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235 Defence, *Supplementary submission 1.1*, p. 14.

236 A draft copy of the letter sent to participants with information on vortex keratopathy was included in the following submissions: Defence, *Submission 1*, Annex I, [pp. 180–181]; Name withheld, *Submission 47*, Annex B.

237 *Committee Hansard*, 11 October 2018, p. 54.

238 Defence, *Supplementary submission 1.1*, p. 9.

239 Defence, *Supplementary submission 1.1*, p. 9. The submission provided additional details on the testing.

240 *Proof Committee Hansard*, 5 November 2018, p. 34.

241 Name withheld, *Submission 56*, [p. 1].

242 *Committee Hansard*, 31 August 2018, pp. 8, 16–17.

243 *Submission 1*, p. 24.

244 *Proof Committee Hansard*, 30 August 2018, p. 32; *Submission 72*, [p. 3].

> I completed the trial documents. They were forwarded away and that was it—I didn't hear a thing afterwards. No-one came to me and said, 'You've been reporting headaches and nausea; let's see what's going on with it.' That was it; it was up to me to look after myself.[245]

3.109 In contrast, Defence stated '[a]ll participants were followed up for 12 months after completion of the eradication course'.[246]

General healthcare available to ADF members

3.110 Submitters did not appear to consider general health services to count as trial follow up:

> There was no specific test or survey conducted for soldiers with regards to assessing their mental health following the drug trial…All soldiers returning from East Timor conducted post screening psychology interviews but I believe this was in no way linked to the drug trial...[247]

3.111 Nevertheless, trial participants (including those who ceased the trial early) would have had access to the range of healthcare services available to ADF members. Defence detailed the comprehensive health services available to all members (including trial participants) throughout their service careers, including:

- return to Australia medical examinations at the end of deployments;
- Return to Australia Psychological Screen (RtAPS) (questionnaire and screening interview);
- post-deployment assessments conducted three months after return to Australia;
- Post Operational Psychological Screening (questionnaire and screening interview) between three and six months after RtAPS;
- general GP services;
- access to psychology and mental health services;
- annual health assessments (prior to 2011), now periodic health assessments; and
- separation health assessments, including formal psychological screening.[248]

3.112 Following separation from the ADF, veterans can access the ADF post-discharge GP health assessment, and other services through DVA.[249] The next chapter includes more information on services available to veterans.

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245 *Proof Committee Hansard,* 5 November 2018, p. 27.

246 *Submission 1*, p. 25.

247 Name Withheld, *Submission 47*, p. 4.

248 *Submission 1*, pp. 28–29.

249 Defence, *Submission 1*, p. 29.